Remarks

Introductory Comments:

Claims 1-18 were examined in the Office Action dated June 10, 1997 and rejected under (1) 35 USC §102(b), as anticipated by U.S. Patent No. 5,446,024, to Builder et al. ("Builder") (claims 1-12, 14 and 16-18); and (2) 35 USC §103, as obvious over Builder (claims 1-18). These rejections are believed to be overcome in part by the above amendments and are otherwise traversed for the reasons discussed below.

Overview of the Above Amendments and New Claims:

Claims 19-46 have been cancelled without prejudice, as being directed to nonelected subject matter. Applicants expressly reserve the right to bring the claims again in a related application.

New claims 47-64 have been added and are directed to alternative embodiments of the invention. Support for the new claims can be found in the original claims filed (see, e.g., claims 1-18) as well as throughout the specification. Thus, no new matter has been added to the application by way of the amendments.

Rejections Over the Art:

Claims 1-12, 14 and 16-18 were rejected under 35 USC §102(b), as anticipated by Builder. The Action states:

> "In Builder's process, a mixture containing IGF-I and its variants is loaded onto a reversed-phase liquid chromatography column....This process can be preceded by a hydrophobic-interaction chromatography step....Examples of suitable reducing agents used in the buffer in his invention include dithiothreitol and urea....He teaches that suitable expression hosts for IGF-I include yeast such as S. cerevisiae and P. pastoris..."

Office Action, pages 3-4, bridging paragraph. However, applicants do not agree that their claimed method is anticipated by Builder.

In particular, claim 1 is directed to a method for producing an authentic, properly folded IGF polypeptide from a yeast cell medium which comprises the IGF polypeptide. The method comprises the following ordered steps: (a) performing a first cation exchange chromatography with the yeast cell medium to yield a first IGF mixture; (b) denaturing and renaturing IGF species present in the first IGF mixture to yield a second IGF mixture; (c) subjecting the second IGF mixture to hydrophobic interaction chromatography to yield a third IGF mixture; and (d) performing reverse phase high performance liquid chromatography on the third IGF mixture to yield a fourth IGF mixture. New claim 47 has similar ordered steps. Builder, however, nowhere teaches or suggests the order of steps set forth in applicants' claims. In fact, Builder does not disclose or suggest performing a denaturing and renaturing step between a cation-exchange column step and a hydrophobic interaction chromatography step. Since no such disclosure is present in Builder, Builder cannot anticipate the present claims.

Neither is Builder believed to render the instant claims obvious. In particular, Section 2142 of the MPEP sets forth the following basic requirements for *prima facie* obviousness: (1) there must be some suggestion or motivation to modify the reference; (2) there must be a reasonable expectation of success (for the modification); and (3) the prior art reference must teach or suggest all of the claim limitations. Furthermore, the teaching or suggestion and the reasonable expectation of success must both be found in the prior art, not in applicants' disclosure. Applicants

submit that the Office has failed to satisfy each of these criteria and has thus failed to establish *prima facie* obviousness.

In this regard, the Action asserts that it would have been obvious "to produce properly folded IGF-I from yeast cell medium using the method taught by Builder." However, Builder only mentions the use of yeast as a host cell in passing. Builder's examples are directed to the production of protein in *E. coli*, a bacterial host. It is well known in the art that the choice of a particular host cell, e.g., a yeast host versus a bacterial host, has a significant impact on the final form and yield of the protein products. This, in turn, affects the particular purification method used to isolate the protein.

More particularly, the two expression systems lead to protein products having different physical forms. Applicants' claims are directed to purification of an IGF from a "yeast cell medium" since the yeast systems used to express the IGF proteins of the present invention secrete IGF directly into the medium. Builder, on the other hand, explains at column 26, line 43, that with his *E. coli* expression system, the "majority of IGF-I is found in the periplasmic space." The physical form of IGF species present in a yeast cell medium would be expected to be different than IGF species packaged in the periplasmic space. Any purification scheme used by Builder must include steps to remove protein species from the periplasmic space which, in turn, creates even different IGF variants. Indeed, a review of Builder's purification protocol shows that an in-situ solubilization step is performed at the end of fermentation and prior to further purification. See, column 24, lines 5-27, of Builder. Builder's purification scheme cannot be practiced directly on the host cell medium.

It is readily apparent that the purification of IGF from *E. coli* poses very different problems than the purification of yeast-expressed and secreted IGF and would result in different protein variants than those obtained with yeast expression systems.

Further, *E. coli* lacks eucaryotic glycosylation systems while yeast can carry out postranslational modification of proteins. See, *Molecular Biology and Biotechnology -- A Comprehensive Desk Reference*, Meyers, R.A., ed. (VCH Publishers, Inc. 1995) pages 309-310 (enclosed). Additionally, yeast systems have different proteases than those found in *E. coli* expression systems. See, e.g., column 7, lines 29-47 of Builder, where it is explained that an *E. coli* strain with reduced proteolytic activity is preferred. Thus, the production of IGF in a yeast host would be expected to result in different IGF variants, including different clipped and glycosylated species, than those recombinantly produced in a bacterial host.

As explained in the specification at page 14, lines 20-26, during fermentation in yeast, a variety of IGF forms are secreted into the medium, including analogs, degraded or nicked monomeric forms, oxidized and glycosylated monomers, numerous multimeric forms, such as dimers, trimers, etc., as well as a major misfolded species which is a disulfide bonded isoform of IGF. Also present after expression in yeast systems is a met-oxidized/glycosylated species (see page 32, line 9 of the specification). Builder, at column 3, lines 27-30 explains that the major IGF variants produced upon expression in *E. coli* are a methionine-sulfoxide variant of properly folded IGF, a misfolded IGF and its respective methionine sulfoxide variant. No mention is made of any glycosylated variants, nor would any be expected to

be present. It is readily apparent that expression in *E. coli* versus expression in yeast would be expected to result in widely divergent IGF species. Therefore no analogy with respect to purification procedures from one system to the other, can be made.

Finally, as explained above, Builder nowhere discloses or suggests applicants' unique combination of elements. Additionally, there is no suggestion to modify Builder's method to that of applicants' and no indication that Builder's method would be successful for purifying a protein from a yeast host cell.

Without a suggestion to modify the reference evident in the prior art, the only conclusion supported by the record is that the rejection was made impermissibly using hindsight reconstruction of the invention. As stated by the Court of Appeals for the Federal Circuit, "[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992). See, also, *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988): "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."

Thus, applicants submit that the claimed invention is nonobvious over the art and request reconsideration and withdrawal of this ground of rejection.

Conclusion

Applicants respectfully submit that the claims as amended define an invention which is novel and nonobvious over the art. Accordingly, allowance is believed to be in

order and an early notification to that effect would be appreciated.

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